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April 4, 2000

MEMORANDUM

SUBJECT: ***CHLORPYRIFOS*** - Re-evaluation Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Deborah Smegal, Risk Assessor
Reregistration Branch 3
Health Effects Division (7509C)

PC Code: 059101

In March 1999, the Health Effects Division (HED) FQPA Safety Factor Committee (FQPA SFC) recommended that a safety factor of 3X should be used in the risk assessment of chlorpyrifos. A re-evaluation of this recommendation was conducted by the FQPA SFC on January 24, 2000. The new evaluation was undertaken in order to consider the possible impact of new hazard information received in the last year. At the January 24th meeting, however, the Committee members were unable to reach consensus on the safety factor recommendation. Subsequently, arguments for retention of the safety factor at 10X or reduction of the safety factor to 3X were presented, with supporting information for review, to the OPP Division Directors and several Agency senior scientists at a February 7, 2000 meeting. The Division Directors and senior

scientists (hereafter referred to as the DD-SS group), concluded that the FQPA safety factor should be retained at 10X for the protection of infants and children to exposure resulting from chlorpyrifos. This memorandum represents documentation of both the January 24, 2000 FQPA SFC meeting and the February 7, 2000 DD-SS meeting.

cc: P. Fenner-Crisp
K. Davis
J. Fleuchaus
J. Housenger
J. Jones
D. Keehner
C. Kimmel
M. Mulkey
S. Makris
L. Rossi
M. Stasikowski
S. Sterling

Background

The FQPA Safety Factor Committee (FQPA SFC) met on January 24, 2000 to re-evaluate the hazard and exposure databases for chlorpyrifos (along with the conclusions of the Jan. 20, 2000 HIARC meeting) in order to make the FQPA safety factor recommendation for use in human health risk assessment. No final safety factor recommendation was made as the FQPA SFC could not reach consensus. Accordingly, the Committee developed arguments for retaining the safety factor at 10X and for reducing the safety factor to 3X (there was no support for raising or removing the factor) and requested the guidance of the OPP Division Directors in determining the FQPA factor to be used in risk assessment for chlorpyrifos.

In response to the request of the FQPA SFC, a meeting was held with OPP Division Directors, the OPP Senior Science Advisor, and several Agency senior scientists (the DD-SS group) on February 7, 2000 to review the two arguments and the supporting information presented to the FQPA SFC.

I. Hazard Identification Assessment Review Committee Meeting - January 20, 2000

Since March 1999, when the FQPA safety factor recommendation was made for chlorpyrifos, much new information has been made known to the Agency by the registrant and through the public comment process (refer to the Report of the Hazard Identification Assessment Review Committee for the meeting held to re-evaluate Chlorpyrifos on Jan 20, 2000).

The HIARC convened on January 20, 2000 to review the additional toxicity data received since its previous review of Chlorpyrifos in February, 1999. These data included: statistical analysis of the morphometric data on the offspring brains (both sexes) at the mid-dose in the developmental neurotoxicity study (as requested by the HIARC after the 1999 review); additional literature data which have been published or are in press since the 1999 meeting; registrant-sponsored developmental studies conducted with the major metabolite of chlorpyrifos (as well as of chlorpyrifos-methyl and triclopyr), 3,5,6-trichloro-2-pyridinol (TCP); and a study on cholinesterase inhibition in neonates and adult male rats treated with acute or repeated oral doses of chlorpyrifos.

The HIARC evaluation of the statistical analysis of the morphometric data, which was submitted by the registrant in response to a request by the HIARC in 1999, indicate that there is a qualitative difference (i.e., differential susceptibility) between the maternal and developmental responses in the developmental neurotoxicity study in rats at the mid (1 mg/kg/day) and high (5 mg/kg/day) doses. Since there has been no similar analysis done for the lowest dose (0.3 mg/kg/day), it is not known if a qualitative difference exists at this dose as well. The HIARC has now requested that an analysis of the morphometric data at the 0.3 mg/kg/day dose level be conducted by the registrant.

A study by Zheng et al. (currently in press) reaffirms the increased sensitivity observed by Moser and Padilla (1998a) following a single, but not repeated, oral exposure to neonatal or juvenile rats (i.e., when determining the dose needed to induce the same percentage reduction in cholinesterase enzyme activity). However, the Zheng study revealed that this increased sensitivity occurred at lower doses (i.e., 0.45 to 1.5 mg/kg for neonates vs. 1.5 to 7.5 mg/kg for adults) than those tested by Moser and Padilla, 1998a (i.e., 15 mg/kg/day in juveniles and 75 mg/kg/day in adults). The Moser and Padilla findings had contributed to the conclusion for the need for retention of an FQPA safety factor (3X) in March 1999.

The results of the studies contained in the literature review by Slotkin et al. (1999) also indicate a differential susceptibility of the developing rat brain to chlorpyrifos. There were clear effects on key cellular processes (e.g., DNA synthesis, cell-cell communication) that are needed for normal brain development. These findings are generally consistent with those from the developmental neurotoxicity study. The human health implications of these biochemical, cellular, and morphological effects are not understood but raise concern. The HIARC concluded that the results reported in the literature review by Slotkin et al., 1999 provide qualitative support for the morphometric findings of the brain in the developmental neurotoxicity (DNT) study and suggest that the inhibition of ChE may not be essential for adverse effects on the brain to occur.

On January 20, 2000 the HIARC further concluded that quantitative and qualitative evidence for increased sensitivity and susceptibility was seen in rabbit fetuses following in utero exposure to TCP in a guideline prenatal developmental toxicity study. Quantitative evidence was demonstrated since the developmental NOAEL (25 mg/kg/day) and LOAEL (100 mg/kg/day) are lower than the maternal NOAEL (100 mg/kg/day) and LOAEL (250 mg/kg/day). Qualitative evidence was demonstrated by the severity of the effects seen in the fetuses (increased incidences of hydrocephaly and dilated ventricles of the brain) compared to minimal toxicity seen in maternal animals (non-statistically significant decreased body weight gain).

II. FQPA Safety Factor Committee Meeting - January 24, 2000

On January 24, 2000, the FQPA Safety Factor Committee concluded that the new findings reaffirm the earlier observation and concern that there is an increased sensitivity of offspring compared to the adults for cholinesterase inhibition following acute exposures to chlorpyrifos. This concern is enhanced by the fact that the new data show that this difference occurs at lower doses than those previously reported. The Committee members agreed that the Zheng et al., 2000 study (in press) showed increased sensitivity following a single oral exposure to neonates at lower doses (i.e., 0.45 to 1.5 mg/kg for neonatal rats vs. 1.5 to 7.5 for adult rats) than those tested by Moser and Padilla, 1998a (i.e., 15 mg/kg/day in pups vs. 75 mg/kg/day in adults).

The Committee also concluded that there is a qualitative difference (i.e., differential susceptibility) between the maternal and developmental responses observed in the developmental neurotoxicity study in rats (cholinesterase inhibition in the dams versus structural effects on the developing brain

of the offspring). In the developmental neurotoxicity study, there were significant dose- and treatment-related decreases in measurements of the parietal cortex in female offspring that were observed at postnatal day 66. Due to the lack of morphometric data for low-dose female rats at postnatal day 66, a definitive offspring NOAEL and LOAEL cannot be determined. Nonetheless, the existing data demonstrate a clear qualitative difference in response between the adult female rats and their offspring, and contribute to a high degree of concern regarding the potential effect of chlorpyrifos exposure on infants and children (toxicity is expressed as cholinesterase inhibition in maternal animals whereas toxicity in the offspring is expressed as structural alterations in brain development). This finding at the mid-dose brings a new uncertainty to light (a lack of a NOAEL) since these morphometric measurements have not been made at the low dose (0.3 mg/kg/day).

There was also concern for the results of the studies contained in the literature review by Slotkin et al. (1999) which indicate a differential susceptibility of the developing rat brain to chlorpyrifos. Some of the data described indicate that the structural effects on the offspring brain observed in these studies and in the developmental neurotoxicity study in rats might occur in the absence of cholinesterase inhibition.

Further Committee considerations included:

- The quantitative and qualitative evidence of increased sensitivity and susceptibility in the offspring compared with the dams as observed in the prenatal developmental study in rabbits with TCP, the major metabolite of chlorpyrifos (as well as of chlorpyrifos-methyl and triclopyr).

- The lack of actual residue data (i.e., in food, drinking water and for other non-occupational exposure scenarios) for TCP resulting from the use of chlorpyrifos and the prevalence of TCP as evidenced in the new Dow AgroSciences and other human bio-monitoring studies. In 1998, Dow AgroSciences evaluated the presence of 3,5,6-trichloro-2-pyridinol (TCP), the primary chlorpyrifos and chlorpyrifos-methyl metabolite, in the urine of 416 children, ages 0-6 yrs in North and South Carolina. TCP was detected in 100% of the children's urine.

- The assessments for the most significant exposures to chlorpyrifos are well-characterized relative to many other compounds (actual data are available for dietary food and residential exposure assessments; dietary water exposure assessment was based on some national monitoring data; acute/chronic dietary risk assessments are very refined and state-of-the-art techniques are used for some residential scenarios). In those cases where data are lacking or are incomplete for residential exposure scenarios, the DRAFT SOPs for Residential Exposure Assessments (using upper-percentile assumptions) are used to estimate the potential exposure. The exposure assessments for residential scenarios which currently have no method of evaluation (i.e., track-in residues, etc.) are expected to be minimal relative to the most significant exposure scenarios (such as post-application

exposure to treated lawns/turf). Although sufficient information is available to determine that exposure to chlorpyrifos would not be substantially underestimated, some uncertainty exists, particularly with regard to the importance of exposure to TCP, as noted above.

- Several comments filed with HED by the registrant for chlorpyrifos, Dow AgroSciences, suggesting that an additional safety factor was unnecessary to protect infants and children. These comments were not found to be persuasive (for complete responses to comments refer to the risk assessment document for chlorpyrifos).

The final safety factor recommendation was not made at this meeting since the Committee could not reach consensus. The arguments for retaining the safety factor at 10X and for reducing the safety factor to 3X (there was no support for raising or removing the factor) were forwarded to the OPP Division Directors to determine the FQPA factor to be used in risk assessment for chlorpyrifos.

III. OPP Division Directors and Senior Scientist Meeting - February 7, 2000

The OPP Division Directors and Agency senior scientists (DD-SS group) met on February 7, 2000 to consider the information reviewed by and the deliberations of the FQPA SFC at the January 24th meeting. This group considered all of the information provided by the FQPA SFC and considered the following points to be key:

- The Zheng et al., 2000 study (in press) showed increased sensitivity following a single oral exposure to neonates at lower doses than those tested by Moser and Padilla, 1998a. The increased sensitivity of neonates observed at lower doses decreased the uncertainty surrounding the differential sensitivities among neonates, juveniles, and adults.

- The additional analyses of the developmental neurotoxicity study and the review of studies reported in the literature reinforced and extended earlier concerns for the susceptibility of the fetus or neonate to potential developmental effects following exposure to chlorpyrifos. The lack of the low dose morphometric data for female adult offspring in this study resulted in uncertainty regarding the offspring NOAEL and potential age-related quantitative susceptibility at this dose.

- The DD-SS group shared the concern for the possibility that the observations in the developmental neurotoxicity study might not be solely attributable to cholinesterase inhibition and acknowledged that this raises an uncertainty in the evaluation of the potential hazards associated with chlorpyrifos.

The DD-SS group concluded that the new evidence for the increased sensitivity at relatively low doses of chlorpyrifos of the young compared to adults and the heightened concerns for the potential susceptibility of the young to the developmental effects of chlorpyrifos warranted the retention of the 10X FQPA safety factor.

IV. Conclusions

In March 1999, the FQPA SFC concluded that an FQPA safety factor was needed due to concern for increased sensitivity seen at high doses and for the qualitative increased susceptibility occurring at the high dose in the developmental neurotoxicity study. Nonetheless, the FQPA safety factor was reduced to 3X because of lack of data addressing whether or not these differences would also occur at lower doses.

In February 2000, new data demonstrated that this was not a high dose phenomenon since:

- increased sensitivity following a single oral exposure to neonates was seen at substantially lower doses; and
- a clear qualitative difference in response (i.e., susceptibility) between adult rats and their offspring was demonstrated in the developmental neurotoxicity study.

The new data also gave rise to uncertainties such as:

- the suggestion that the inhibition of cholinesterase may not be essential for adverse effects on brain development; and
- the lack of an offspring NOAEL in the DNT based upon structural alterations in brain development as the toxicity endpoint of concern.

Therefore, the DD-SS group concluded that their evaluation of the available hazard and exposure databases for chlorpyrifos, including the information received and reviewed in the past year, results in an overall ***higher*** degree of concern regarding the potential consequences of chlorpyrifos exposure to infants and children than was determined during the FQPA safety factor evaluation in March 1999. Consequently, they recommended that the FQPA safety factor should be **Retained at 10X** for the protection of infants and children to exposure resulting from the use of chlorpyrifos.

The FQPA SFC determined that the FQPA safety factor would be applicable to **Females 13-50** and **Infants and Children** population subgroups for **all exposure durations**:

> Acute Dietary Assessment - The FQPA safety factor is applicable for Females 13-50 and Infants and Children population subgroups due to the concern that adverse effects could result from a single exposure to chlorpyrifos (as demonstrated in several open literature studies including Zheng et al.).
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> Chronic Dietary Assessment - The FQPA safety factor is applicable for Females 13-50 and Infants and Children population subgroups due to the concern that adverse effects could result from repeated exposure to chlorpyrifos (as demonstrated, for example, in the developmental neurotoxicity study in rats).

Residential and other Non-occupational Exposure Assessment - The FQPA safety factor is applicable for Females 13-50 and the Infants and Children population subgroups for all exposure durations due to the adverse effects resulting from single or repeated exposure(s) to this organophosphate insecticide in or around residential (non-occupational) settings.